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Review that questioned serotonin theory of depression was flawed, say researchers

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A group of scientists have said a review which concluded there was no consistent evidence of a relationship between serotonin and depression was biased and seriously flawed.[1]

Last July a systematic umbrella review, published in *Molecular Psychiatry*, concluded "there is no convincing evidence that depression is associated with or caused by lower serotonin concentrations or activity" and questioned the reasons behind high prescribing rates of antidepressants.[2 3]

Writing in the same journal, 36 researchers have criticised the paper saying there were methodological weaknesses in the review process, selective reporting of data, oversimplification, and errors in the interpretation of neuropsychopharmacological findings.

Lead author of the comment piece, Sameer Jauhar, senior clinical lecturer in affective disorders and psychosis at the Institute of Psychiatry, Psychology, and Neuroscience (IoPPN) at King's College London, said the authors "presented no new analyses of the data, used their own criteria for assessing research quality, interpreted findings differently from the original research, and made fundamental errors pertaining to the scientific method."

The 2022 review was methodologically flawed and inconsistent with the conventional umbrella review process, the comment says. Unlike most umbrella reviews, where authors extract data and analyse them themselves the authors summarised existing results with no new analysis.

The comment authors say that umbrella reviews are supposed to guard against citing papers based on authors' preferences but this review included selective individual studies. The criteria for grading the quality of evidence were arbitrarily set by the authors, they say.

They also say that the authors appear to have ignored studies showing a link between serotonin and depression. They point out that some of the most robust evidence linking the serotonin system to depression comes from studies where the levels of one of the precursors of serotonin—tryptophan—are lowered. The comment says the authors misreported one review emphasising that tryptophan depletion does not cause depression symptoms in healthy volunteers with little mention of effects in those with depression.

Another criticism is that the 2022 review misrepresents and misinterprets molecular imaging data of serotonin transporter binding.

Oversimplification

A position statement from the Royal College of Psychiatrists published in 2019 said, "The original idea that antidepressants 'correct a chemical imbalance in the brain' is an oversimplification, but they do have early physiological effects and effects on some aspects of psychological function."[4]

Psychiatrists have always thought the chemical imbalance theory of depression was a simplistic view, used to explain how brain changes occur in depression in a more accessible way, said Allan Young, head of academic psychiatry at IoPPN and one of the authors of the comment piece. "The biopsychosocial model of psychiatric disorders was developed by psychiatrists and acknowledges that there are biological, genetic, psychological, and social influences on depression, which need to be assessed in order to help patients. Any criticism of the chemical imbalance theory truly misunderstands why it was developed and used by researchers and clinicians. Nevertheless, brain changes do occur in depressed people, including changes in serotonin, and thus the conclusion that this 2022 umbrella review reaches are incorrect."

Antidepressant drugs

Last year NICE published its first guideline in 12 years on managing depression in adults and recommended offering a range of evidence based treatment options to patients—from psychological therapies to antidepressants.[5]

Carmine Pariante, a co-author of the commentary and expert in the neurobiology and treatment of depression, also from IoPPN, said, "Perhaps the worst flaw of the 2022 review is that it casts doubts on the effectiveness of antidepressant drugs, without presenting any evidence in support of this conclusion. There is incontrovertible evidence that antidepressant drugs are effective in treating people with clinically significant depression. The decision to use antidepressants, with or without psychological therapy, is taken by the person with depression jointly with their treating physician."

1 Jauhar S, Arnone D, Baldwin DS, etal. A leaky umbrella has little value: evidence clearly indicates the serotonin system is implicated in depression. *Mol Psychiatry* 2023;•••.
doi: 10.1038/s41380-023-02095-y. pmid: 37322065

2 Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol Psychiatry* 2022.
doi: 10.1038/s41380-022-01661-0. pmid: 35854107

3 Wise J. "No convincing evidence" that depression is caused by low serotonin levels, say study authors. *BMJ* 2022;378:.
doi: 10.1136/bmj.o1808 pmid: 35853814

4 Royal College of Psychiatrists. Position statement on antidepressants and depression. May 2019. www.rcpsych.ac.uk/docs/default-source/improving-care/better-mh-policy/position-statements/ps04_19-antidepressants-and-depression.pdf.

5 NICE. Depression in adults: treatment and management. June 2022. www.nice.org.uk/guidance/ng222.